REMARKS/ARGUMENTS

Claim 28 is pending in this application. No new matter is added.

Rejections under 35 U.S.C. §112, First Paragraph

Claim 28 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the specification does not disclose how to use the claimed method to treat or prevent atherosclerosis in humans *in vivo* using an oral tolerance inducing amount of oxidized LDL. The Examiner further states that it is unpredictable whether human disease can be treated via inducing oral tolerance to a disease antigen. *See*, Office Action at pages 2-6. In support of the rejection, the Examiner recites *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) factors (5), (7), (3) and (2) against claim 28 at pages 3-4 of the Office Action. Applicants traverse.

State of the Prior Art (Wands Factor 5) and Predictability or Unpredictability of the Art (*Wands* Factor 7)

The Examiner states that regarding *Wands* factors (5) and (7), there is a high unpredictability in the art. Specifically, the Examiner cites Spack et al. *Expert Opin. On Invest. Drugs*, 6:1715-1727, 1997 ("Spack") and McKown et al., *Arthritis and Rheum.* 42:1204-1208, 1999 ("McKown") to show that it is unpredictable whether human disease can be treated via the induction of oral tolerance to a disease antigen. *See*, Office Action at pages 4-5.

Applicants submit that pending claim 28 does not recite or require the induction of oral tolerance as stated by the Examiner. In fact, claim 28 is not directed to the induction of oral tolerance at all; rather, claim 28 is directed to a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration. As such, the Examiner's arguments regarding the unpredictability of disease treatment via inducing oral tolerance to a disease antigen, including the discussion of McKown and Spack is misplaced and improper.

Applicants have previously argued in the December 7, 2005 Amendment and Response, August 31, 2006 Amendment and Response and the In-Person-Interview conducted on November 15, 2005 that the claims are directed to treating atherosclerosis and do not recite or require the induction of oral tolerance. However, the Examiner has stated that although the claims are not directed to a specific mechanism of action, the disclosure indicates that the claimed method works via oral tolerance and that the disclosure is sufficient to maintain the enablement rejection under 35 U.S.C. §112, first paragraph. *See*, Office Action at page 5.

The Examiner's assertion is incorrect. It is well recognized under U.S. law, that it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works. *Newman v. Quigg,* 877 F.2d 1575, 1581 (Fed. Cir. 1989). It is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how the invention works a necessary element in the specification to satisfy the enablement requirement. *Fromson v. Advance Offset Plate, Inc.,* 720 F.2d 1565, 1570 (Fed. Cir. 1983). A patent applicant need only teach how to achieve the claimed result, even if the theory of operation is not correctly explained or even understood. *In re Isaacs,* 347 F.2d 887, 892, 146 USPQ 193, 197 (C.C.P.A. 1965). Applicants submit that the instant application discloses a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration and thus satisfies the how-to-use requirement of 35 U.S.C. §112, first paragraph, irrespective of whether the claimed method works via oral tolerance or another unidentified mechanism.

The Presence or Absence of Working Examples (*Wands* Factor 3)

The Examiner states that regarding *Wands* factor (3), while the specification provides an example in a mouse model, there were copious amounts of mouse research that suggested that while oral tolerance could be used to treat multiple sclerosis and rheumatoid arthritis in such models, said diseases were not successfully treated in humans using oral tolerance. The Examiner again cites McKown and Spack to support this assertion. *See*, Office Action at pages 2-5.

As described *supra*, claim 28 is not directed to the induction of oral tolerance and is not directed to the treatment of multiple sclerosis or rheumatoid arthritis and the citation of Spack and McKown is not relevant to the currently recited invention. The instant invention and the additional data generated using the teachings of the specification and reported in the December 7, 2005 Harats § 1.132 Declaration, readily demonstrate to one of ordinary skill in the art how to make and use the present invention to treat atherosclerosis by oral administration of isolated human oxidized LDL.

Specifically, the instant specification and the additional data supplied in the December 7, 2005 Harats § 1.132 Declaration provides a working example that demonstrates the successful treatment of atherosclerosis in an LDL-receptor deficient mouse by oral administration of isolated human oxidized LDL. *See*, Specification at, *e.g.*, page 15, lines 20-29; and page 18, line 18 to page 19, line 31. It is well recognized in the art that the LDL-receptor deficient mouse is the preferred animal model to evaluate the effects of pharmacologic agents on atherosclerosis. LDL-receptor deficient mice, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, August 31, 2006 Harats § 1.132 Declaration at ¶ 5-6.

Specifically, the use of animal models (*i.e.* murine models) to evaluate the effects of pharmacologic agents on atherosclerosis was well recognized in the art when the instant application was filed (*See*, *e.g.*, Bocan, *Curr. Pharm. Des.* 4(1):37-52, 1998); and, the LDL-receptor deficient mouse was recognized in the art as a preferred model of atherosclerosis at the time of the instant application. (*See*, *e.g.*, Ishibashi et al., *J Clin Invest.* 92:883–893, 1993; Lichtman *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 19(8):1938-44, 1999; Maron, R. *et al., FASEB J.* 14:A1199-(Abstr.), 2000). Moreover, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDL-receptor gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

To further support the rejection, the Examiner cites Wouters et al. *Clin. Chem. Lab. Med.* 43(5): 470-479, 2005 ("Wouters") and states that Wouters, discloses that the LDL-receptor mouse displays cholesterol metabolic pathways not found in humans and as a consequence "this

route can serve as a backup mechanism for lipoprotein clearance in LDL-receptor mice, yielding unforeseen side effects." *See*, Office Action at page 6. Although the LDL-receptor deficient mouse is not the optimal model for genetic human familial hypercholesterolemia, it is one of the most predictable models for human atherosclerosis and the likelihood of new molecules to work as anti-atherosclerosis drugs in humans is high (*See*, *e.g.*, Babaei *et al.*, *Cardiovasc Res.* 48(1):158-67, 2000; Burleigh *et al.*, *Biochem Pharmacol.* 70(3):334-42, 2005; Chen *et al.*, *Circulation.* 106(1):20-3, 2002; Collins *et al.*, *Arterioscler Thromb Vasc Biol.* 21(3):365-71, 2001; Cyrus *et al.*, *Circulation.* 107(4):521-3, 2003; Elhage *et al.*, *Am J Pathol.* 167(1):267-74, 2005; Li *et al.*, *J Clin Invest.* 106(4):523-31, 2000; Napoli *et al.*, *Proc Natl Acad Sci U S A.* 99(19):12467-70, 2002, already of record). Human atherosclerotic plaques are infiltrated with lymphocytes and display an inflammatory phenotype that includes expression of pro-inflammatory cytokines. In this sense the LDL-receptor deficient mice have plaques similar to those of humans containing a significant number of lymphocytes (*See*, *e.g.*, Roselaar *et al.*, *Arterioscler Thromb Vasc Biol.* 16(8):1013-8, 1996, already of record). Moreover, therapeutic strategies that apply for atheroprotection in humans are similarly successful in LDL receptor deficient mice and may not be so in ApoE knockout mice (*See*, *e.g.*, Wang *et al.*, *Atherosclerosis.* 162(1): 23-31, 2002, already of record). These findings indicate that plaques developing in LDL receptor deficient mice may be more relevant to human atherosclerosis than other non-human models and thus, it is one of the most widely employed models for drug development in the field of atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

The Amount of Direction or Guidance Presented (*Wands* Factor 2)

The Examiner states that regarding *Wands* factor (2), there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. *See*, Office Action at pages 5-6.

Once again, as described in detail *supra*, claim 28 is not directed to the induction of oral tolerance but rather are directed to a method of treating atherosclerosis by oral administration of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier

Applicants have provided working examples that demonstrate the successful treatment of atherosclerosis by oral administration isolated human oxidized LDL in an LDL-receptor deficient mouse and the LDL-receptor deficient mouse is the most art-recognized model of the biochemical and morphological effects of atherosclerosis. Further, the working examples provide a range of concentrations of the composition to treat atherosclerosis (*See*, *e.g.*, page 18, lines 27-29; page 19, lines 18-19). Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention, would be able to determine the corresponding doses useful in other species, including humans, without undue experimentation. The specification need not disclose what is well known in the art. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 7-8.

As described *supra*, Applicants have provided several working examples, both in the specification and additional data confirming the results described in the specification, and demonstrated successful treatment of atherosclerosis by oral administration of isolated human oxidized LDL. Therefore, Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention would be able to readily determine how to make and use the present invention and respectfully request withdrawal of the instant rejection of claim 28 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §103(a)

Claim 28 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,783,193 to Michael ("Michael") in view of Sima et al., *11th Int. Symp on Atherosclerosis*, page 227, October 1997 ("Sima") and Hansson et al., *11th Symp on Atherosclerosis*, page 289, October 1997 ("Hansson") in view of U.S. Patent No. 6,541,011 to Punnonen ("Punnonen"). Applicants traverse.

Applicants submit that there is no reasonable expectation of success in combining Michael, Sima, Hansson and Punnonen to reach the present invention. As described *supra*, the present invention is not directed to the induction of oral tolerance but rather the treatment of

atherosclerosis by oral administration of isolated OxLDL. These features are not taught or suggested by the combined references.

Michael is fatally flawed. Michael merely teaches oral formulations of therapeutic protein antigens to provide oral tolerance. Michael fails to teach or suggest the treatment of atherosclerosis and, as stated by the Examiner at page 7 of the Office Action, fails to teach or suggest human oxidized LDL. That is, Michael fails to teach or suggest any of the features of the present invention.

The combination of Sima, Hansson and Punnonen fails to cure these fatal deficiencies of Michael. As discussed previously in the record, Sima and Hansson, do not provide any reasonable expectation of success by orally administering an enteric coated composition comprising isolated oxidized LDL to treat atherosclerosis. In contrast, these references clearly teach away from the present invention by teaching that OxLDL contributes to the development of atherosclerosis (*i.e.*, OxLDL is pro-atherosclerotic). *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 10. Thus, the present invention proceeds contrary to the accepted wisdom in the art (the teachings of Sima and Hansson) and these findings are evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Punnonen does not cure these deficiencies of Michael, Sima and Hansson as Punnonen is merely general teaching of the induction of oral tolerance, which is not recited in the instant claims.

The skilled artisan would readily recognize that there is no expectation of success combining Michael, Sima, Hansson and Punnonen to reach the present invention. Specifically, one of ordinary skill in the art would not reasonably expect the oral administration of an enteric coated composition comprising isolated oxidized LDL to treat atherosclerosis. Specifically, OxLDL is ingested on a daily basis as part of a routine diet and OxLDL is degraded in the gut following ingestion. For this reason, Applicants submit that at the time the application was filed one of ordinary skill in the art would not be motivated to combine Michael, Sima, Hansson and Punnonen with a reasonable expectation of success. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 10.

Moreover, Applicants submit that one of ordinary skill in the art would not have expected a composition for oral administration comprising isolated OxLDL to be therapeutically effective for treating atherosclerosis.

The results described in the specification demonstrate that the composition of the claimed invention (enteric coated composition comprising isolated oxidized LDL and a pharmaceutically acceptable carrier for oral administration) displays the unexpected ability to treat atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 10. These results were not taught or suggested in the art at the time of filing the application (including the teachings of Sima and Hansson) as the state of the art at the time of filing readily recognized OxLDL as a major contributory factor for the development and progression of atherosclerosis.

Applicants respectfully request that the § 103 rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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